Assessment of health-related quality of life in cancer clinical trials

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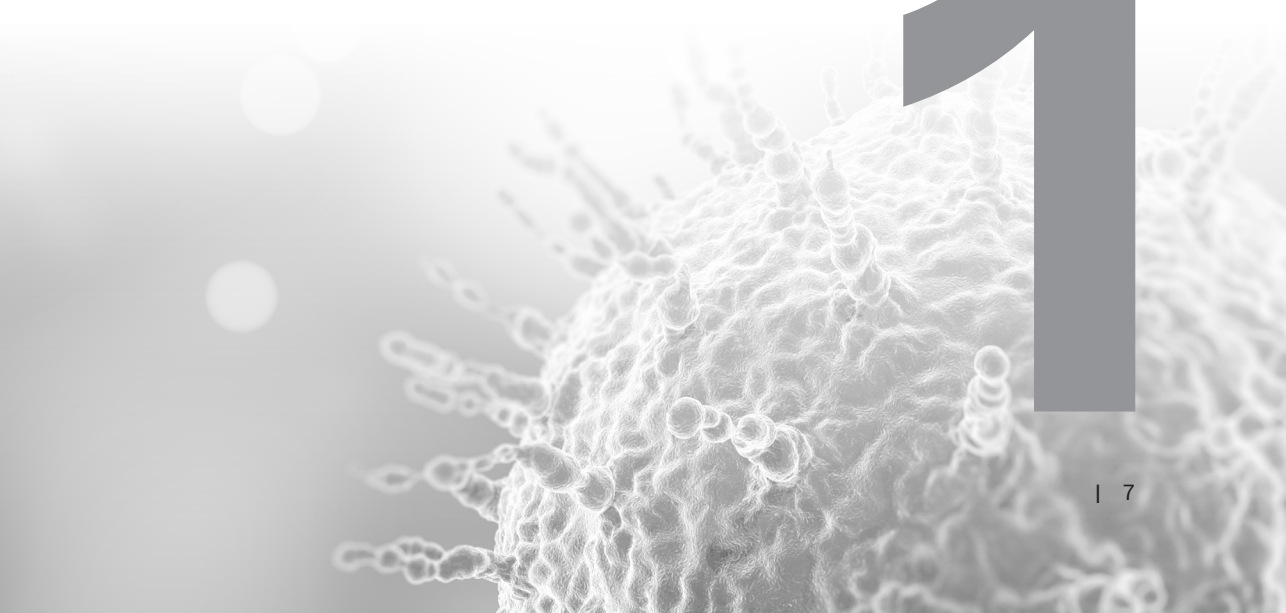
General Introduction



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Cancer is a heterogeneous group of diseases characterized by uncontrolled growth of cells, invasion of cancer cells into neighboring tissues and the spread of these cells to tissues and organs beyond where the tumor originated (i.e. metastasis) [1]. The most common cancers globally in 2018 were lung (2.09 million cases), breast (2.09 million cases), colorectal (1.80 million cases), prostate (1.28 million cases), skin cancer (non-melanoma) (1.04 million cases), and stomach cancer (1.03 million cases).

Cancer is one of the leading causes of death globally in both high- and low-income countries. In 2018, about 9.6 million causes of death were related to cancer [2], of which approximately 70% in low- and middle-income countries. The incidence rates in the 50 selected registries range between 100-400 per 100,000 males and between 100-300 per 100,000 females. Mortality rates in the 50 selected countries range from between 50-200 deaths per 100,000 males and 50-100 deaths per 100,000 females. For both sexes, the highest incidence and mortality rates generally occur in North America, Oceania, and Europe. Figure 1 and 2 depicts the incidence and mortality rates for both sexes respectively.

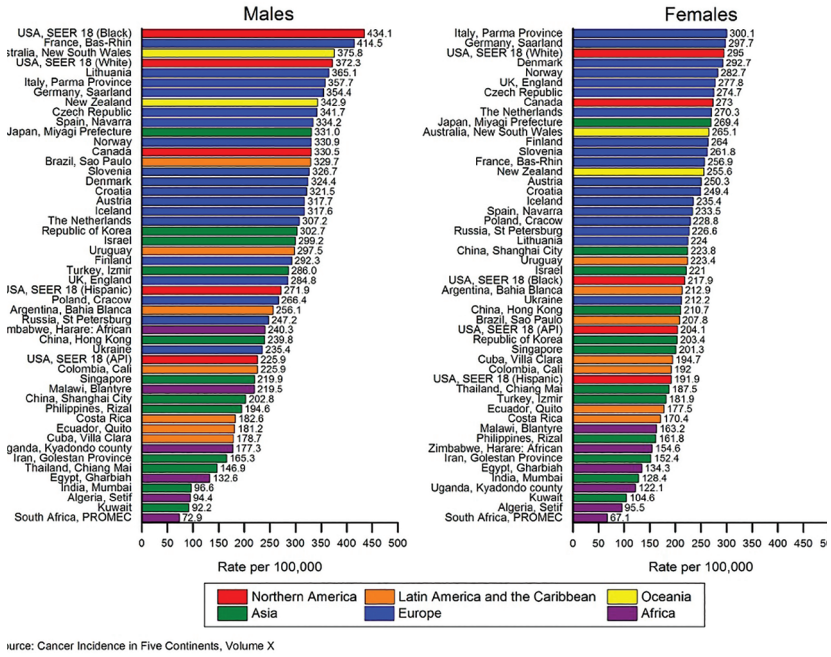
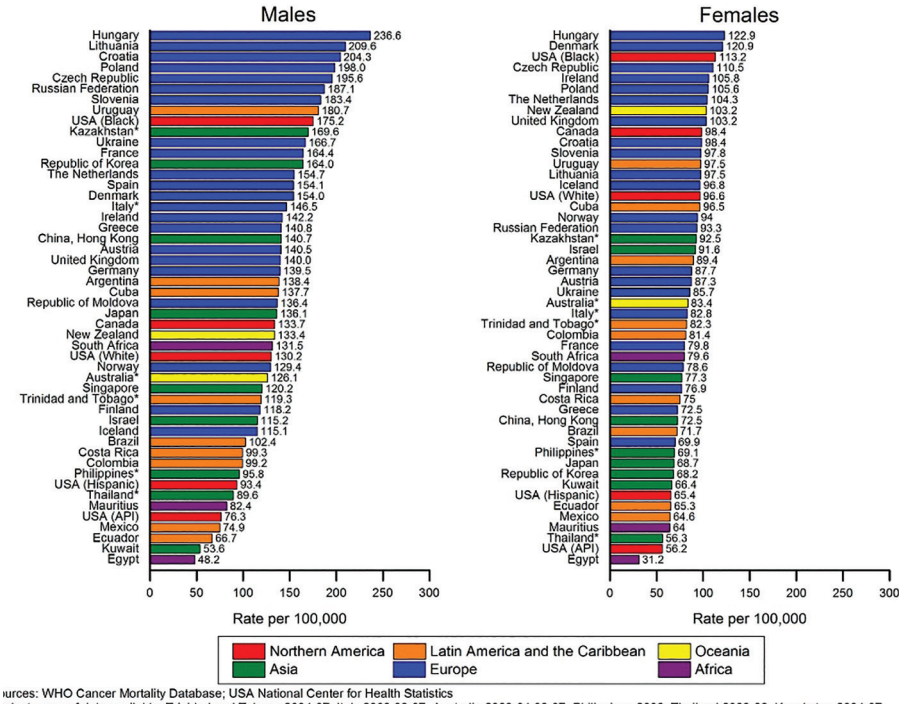


Figure 1. All sites cancer incidence rates by sex in select registries, 2003–2007



ıurces: WHO Cancer Mortality Database; USA National Center for Health Statistics
ɨelect years of data available: Trinidad and Tobago 2004-07; Italy 2003,06-07; Australia 2003-04,06-07; Philippines 2003; Thailand 2003-06; Kazakstan 2004-07.

Figure 2. All sites cancer mortality rates by sex, select countries, 2003–2007

Around one third of cancer diagnoses are due to five leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol use. Tobacco use is the most important risk factor for cancer and is responsible for approximately 22% of cancer deaths [3]. Cancer-causing infections, such as hepatitis and human papilloma virus (HPV), are responsible for up to 25% of cancer cases in low- and middle-income countries [4]. Late-stage presentation and inaccessible diagnosis and treatment are common. In 2017, only 26% of low-income countries reported having pathology services generally available in the public sector, limiting diagnosis and thus treatment. Similarly, more than 90% of high-income countries reported treatment services are available throughout the country compared to less than 30% of low-income countries. The economic impact of cancer is significant: the total annual economic cost of cancer in 2010 was estimated at approximately US$ 1.16 trillion [5]. This societal burden is increasing, as a fundamental factor

for the development of cancer is age. According to cancer researcher Robert A. Weinberg, "If we lived long enough, sooner or later we all would get cancer" [6]. This is likely due to a build-up of risks factors for cancer that increases with age.

There are several ways to treat cancer, depending on the type and disease stage. Treatment options include surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy or a combination of these treatments, as well as stem cell transplantation. The main goal of cancer treatment is to prolong survival, without compromising the patients' functioning and well-being. To determine the net clinical benefit of a treatment strategy, the benefits in terms of prolonged survival should be weighed against the possible negative effects of the treatment on the functioning of patients. It is therefore important to include traditional outcomes such as survival and radiological response in clinical trials, but also clinical outcome measures such as health-related quality of life (HRQOL).

Concept of health-related quality of life

Over the past century, the concept of quality of life has evolved tremendously [7]. Previously, quality of life was referred to as 'having a good life' and deriving 'satisfaction from life'. Today, by contrast, quality of life is defined as a statistical index based on several parameters such as economic, health-related, and environmental-related issues to an individual's or group's life conditions [8]. In 1991, Levine proposed a model of socio-psychological quality of life, which is an "area of human life by which a given person is directly affected, and which is important for him or her and as an individual perception of position in life within the cultural context and the system of values in which a person lives, in relation to the tasks, expectations and standards set by environmental conditions" [9]. Based on the definition by Levine, in 1997 Saxen and Orley isolated those factors that make up an individual's quality of life, including physical health, psychological state, level of independence, relationships with other people, and the environment in which the person lives [10].

Also in the 90's, Schipper and colleagues introduced the concept of quality of life in relation to health, i.e. health-related quality of life (HRQOL) [11,12], which they defined as the "functional effect of disease and its treatment, as perceived (experienced) by the patient". Specifically, they noted that a human's state of

health can significantly influence their life and functioning, and might ultimately have some bearing on any assessment of their quality of life. Accordingly, when assessing quality of life in a medical context, healthcare providers should analyze the impact of the disease and therapy on a patient's life, as subjectively perceived by the patient. In other words, HRQOL can be defined as an index of a patient's perception of his/her own condition in life, in the context of a particular disease and its treatment.

HRQOL is a multidimensional concept and generally comprises four dimensions: physical and motor skills, mental state, social and economic conditions, and somatic perception (i.e., symptoms)[8]. It is important to distinguish between patient's objective state of health (as determined by measured symptoms, e.g. increased blood pressure) and the subjective experience of the patient (e.g. headache as caused by high blood pressure), which requires a different method of assessment. An objective assessment refers to a method of determining a person's actual situation, or the facts independent of the person's subjective opinions or feelings about their particular situation. In contrast, a subjective assessment refers to a method of determining the situation as described by the patient, with sufficient consideration of the emotional dimensions of their experience. This assessment should take into account the full range of psychological states—that is, it is important to not only diagnose negative emotional states such as depression and anxiety, but also the positive components of one's experience, such as satisfaction, hope, and ease of adaptability [13].

Assessment of health-related quality of life in cancer clinical trials

In order to determine the effectiveness of therapeutic procedures, modern oncology should not only consider the factors related to life expectancy, such as progression-free and overall survival, but also the patient's evaluations of his or her functioning and wellbeing, for example assessed with measures of HRQOL [14]. In particular, a patient's HRQOL may be an important measure of treatment effectiveness, particularly for oncological diseases, where prolonged overall survival is not necessarily indicative of satisfactory treatment, and the patient's own HRQOL is not necessarily aligned with the possibility of cure.

Several types of questionnaires are used in cancer clinical trials to assess HRQOL [15] First, there are generic questionnaires that universally evaluate

patients, regardless of their diagnosis. Examples include the Short Form 36 [16] or the WHO Quality of Life-BREF [17]. Second, there are cancer-specific questionnaires, such as the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 [18] and Functional Assessment of Cancer Therapy-General (FACT-G) [19]. Third, disease-specific questionnaires are available to measure issues that are relevant to a specific disease only, e.g. EORTC QLQ-Brain (QLQ-BN20), FACT-Brain and EORTC QLQ lung cancer module (QLQ-LC13) [20].

Relevance of health-related quality of life data in clinical trials

As previously mentioned, in clinical trials it is important to determine the net clinical benefit of a new treatment, in which one should consider both quantity and quality of survival. The latter could be measured with HRQOL instruments, as they provide information on the (possible negative) impact of treatment on the patients' functioning and wellbeing. Information from both sources can be used to inform the research community, policy makers, physicians, and patients in the treatment decision-making process. It is therefore of utmost importance that data on HRQOL is reliable and of high quality.

It may, however, be challenging to interpret findings on both quantity and quality of survival. Currently, survival and HRQOL outcomes are analyzed separately using a longitudinal model for HRQOL scores, and a time-to-event approach for the survival outcome. However, separate analyses of longitudinal data and survival data may lead to inefficient or biased results [5]. Also, when results on survival and functioning are conflicting (e.g. improved survival, but worse HRQOL), it is difficult to decide which treatment to opt for.

In most clinical trials, survival is the primary outcome of interest. One way to estimate survival, while accounting for the (possible negative) impact of the treatment on HRQOL over time, is by modeling these outcomes simultaneously. Theoretically this is possible by including HRQOL as a time-dependent covariate in the survival analysis. However, this model may not be valid because HRQOL data may be missing due to disease progression or death (i.e. informative censoring), or when substantial measurement error occurs. To solve these difficulties, joint models have been proposed [6–25]. Joint models of longitudinal and survival processes can recover information from these potentially informative

censorings [26–28] and also allow the assessment of the effects of factors of interest on the survival and longitudinal HRQOL endpoints simultaneously [6]. A similar approach can be used when HRQOL is the primary outcome in a clinical trial, which is increasingly the case in the last few years. Whether these models result in facilitated interpretation of the net clinical benefit of a treatment strategy remains to be investigated.

Use of health-related quality of life data for prognosis

Role of prognosis in clinical research

Diagnosis of a disease, prognosis of outcome and effectiveness of therapy are key issues in medical practice. Diagnosis is about "determining" disease at a fixed time point with the intent of grouping patients into homogenous disease groups, while prognosis is about "predicting" individual disease status or patient outcome. Diagnosis and prognosis are closely related. In oncology, tumor histology is still widely used for diagnosis, but also has a role in prognosis of outcome. Prognostic factors are identified to explain some of the heterogeneity associated with the expected course and outcome of the disease, which is useful in patient counselling and for therapeutic decision-making, e.g. to avoid over- or undertreatment in patients. Moreover, prognostic factors can be used as stratification factors in randomized clinical trials, as they ensure better balance between treatment groups, thereby facilitating interpretation of treatment effects.

Prognostic factors in cancer patients at the time of diagnosis

Traditional prognostic factors are demographic and clinical variables such as age at diagnosis, sex, performance status, and tumor-related characteristics[1]. The assessment of factors that affect outcome in cancer patients is a very active research area. New molecular factors that are not only of prognostic importance, but also present potential new treatment targets, have created a large interest in prognostic factor analysis. Unfortunately, HRQOL outcomes are not often included in prognostic factor analysis, while they may provide additional information to known prognostic variables. Indeed, inclusion of HRQOL in

prognostic factor analysis is expected to increase the understanding of treatment efficacy and may direct further research.

To date, several studies [21,22] have shown that certain HRQOL domains are independently prognostic of survival in cancer patients, and that HRQOL in addition to clinical data improve survival prediction. However, not all HRQOL domains add predictive information, and the predictive scales/items differ between disease sites. To confirm the association between baseline HRQOL and survival, as well as the added predictive value of HRQOL relative to clinical variables, independent of cancer site, an external validation of these results is necessary in a large pooled dataset, and will be performed in this thesis.

Dynamic predictions during the disease course

Joint models may not only be useful to determine the net clinical benefit of clinical trial results, these models can also be useful in clinical practice. Indeed, for an individual patient at a specific time point during follow-up, all available information (including both baseline information and accumulated HRQOL scores) could be used to produce dynamic predictions of this particular patient's future survival probabilities (individualized treatment) [23]. Access to this information will enable clinicians to gain a better understanding of the disease dynamics and ultimately make the most optimal decision at that specific time point for an individual patient. Whether such an approach is feasible will also be explored in this thesis.

Methodological challenges in assessing health-related quality of life in clinical trials

Time windows

HRQOL may provide valuable information on the impact of cancer treatment, warranting appropriate assessment of HRQOL and correct statistical analysis. However, this appears to be challenging for clinicians, statisticians, and designers of clinical studies. Several appropriate statistical techniques have been described in the literature, including Cox-regression models with HRQOL as (time-varying) covariate to predict survival, linear mixed-effect models [24] and joint modelling [25] to analyze longitudinal HRQOL and combined longitu-

dinal and survival data, respectively, and generalized linear models to analyze cross-sectionally measured HRQOL data [26]. Although appropriate analysis techniques are warranted, other methodological aspects should also be considered before collecting, analyzing and interpreting HRQOL data. One important issue is the timing of HRQOL collection. Osoba pointed out that when studying the effects of a treatment that is cyclic and toxic, the planning and timing of HRQOL assessment has particular relevance [27]. That is, when the goal is to assess the immediate toxicity effect of a treatment, HRQOL should be assessed during this period of acute toxicity and not when the toxicity effect has faded. However, in practice it may be difficult to measure exactly at the pre-specified assessment points, thereby failing to capture the clinically important side effects of new treatments. Indeed, patients may, for some reason, fail to complete the questionnaire at the scheduled time, but then return it by post a few days later. As deviation from the planned assessment schedule is common, and to minimize HRQOL data loss for statistical analysis, so-called completion time windows are often applied. Such a completion-time window considers a certain number of days before and after the scheduled assessment date to be eligible, such that all questionnaires completed within that period are assumed to belong to the actual planned assessment time. Although the timing of HRQOL is very important, the use of completion time windows has received relatively limited attention in the literature. Moreover, it is unknown if the effects of introduction completion time windows are invariant across treatment modalities. In this thesis, it will be evaluated how the application of time windows will impact the interpretation of study outcomes, and may subsequently impact decision-making.

Role of proxies

Another challenge with HRQOL data is that it is patient-reported, i.e. that it reflects the patient's perspective. Although the patients' perspective is leading, in some cases it may be difficult for a patient to complete a HRQOL questionnaire, for example due to a poor health status or cognitive impairments. In that case, a proxy assessment may provide valuable information about the patient's functioning and well-being. A proxy evaluation means that the HRQOL assessment is carried out by another person than the patient, e.g. a relative or physician (i.e. patient-by-proxy perspective), and that the conclusions of the patients'

functioning and wellbeing are estimated by the proxy. Whether patient and proxy assessments are congruent in all situations (e.g. when patients are cognitively impaired) remains to be determined, and will also be subject of this thesis

Aim and outline of this thesis

The primary aim of this thesis is to assess the clinical relevance of collecting HRQOL data in cancer clinical trials and to explore methodological barriers in the collection and analysis of HRQOL data. The results of this thesis may be useful for clinicians when designing, analyzing and interpreting HRQOL findings obtained in cancer clinical trials.

In part 1, the clinical relevance of HRQOL assessments in cancer clinical trials is explored. Chapter II addresses the prognostic value of baseline HRQOL scores for overall survival in a heterogeneous group of cancer patients. In Chapter III, it is evaluated whether a change in HRQOL scores from baseline to the first follow-up visit, rather than the baseline score alone, is prognostic for overall survival in patients with lung cancer. Lastly, in Chapter IV it is explored whether joint-modelling of longitudinally collected HRQOL data and survival data in primary brain tumor patients results in a better estimation of the treatment effect on survival, and how we can use joint-modelling to predict individual patient's overall survival.

In part 2, methodological barriers in assessing HRQOL in cancer clinical are explored. Chapters V and VI address the challenges centered around the timing of collecting HRQOL data during chemotherapy and radiotherapy respectively, and how this might affect the treatment outcome. Lastly, in Chapter VII it is explored whether HRQOL data reported by patient's proxy is reliable and in agreement with the patient's reporting, and is therefore suitable as substitution in case of missing data.

Finally, in part 3, a summary and discussion of the main findings is provided, together with future directions.